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A study to evaluate the safety, tolerability, processing by the body, and antitumor activity of inavolisib and paclitaxel

Submission date 18/05/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 07/07/2021	**Overall study status** Completed	
Last Edited 19/09/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
This study will evaluate the safety (side effects), how the body processes the treatment (pharmacokinetics), what the treatment does to the body (pharmacodynamic effects), and preliminary anti-cancer activity of the drug inavolisib given in combination with the drug paclitaxel in patients with locally advanced or metastatic solid tumors, and of inavolisib given in combination with paclitaxel, in patients with locally advanced or metastatic PIK3CA-mutated (altered gene), HER2-positive breast cancer. Locally advanced cancer is cancer that has spread only to nearby tissues or lymph nodes, while metastatic cancer is cancer that has spread to other parts of the body.

Who can participate?
Part 1, Arm A: Patients aged 18 years and over with locally advanced or metastatic solid tumors
Part 2, Arm A: Patients aged 18 years and over with locally advanced or metastatic PIK3CA-mutated cancer

What does the study involve?
Up to 104 patients at various hospital locations around the world will take part in this study. The study is divided into two parts. Part 1, Arm A is the dose-escalation (dose-finding) part of the study. Part 2 consists of Arm A which will be treatment expansions after dose-finding is complete.
Part 1, Arm A: inavolisib will be tested at different doses and schedules in combination with paclitaxel in up to 24 patients with locally advanced or metastatic cancer
Part 2, Arm A: a dose and schedule of inavolisib determined to be safe in Part 1, Arm A will be tested in combination with paclitaxel, in about 80 patients with locally advanced or metastatic PIK3CA mutated (altered gene) cancer.
Patients will have the following assessments and measurements:
1. Vital signs - temperature, pulse rate, blood pressure, breathing rate and oxygen level
2. Complete or limited physical exam
3. Assessment of performance status
4. Electrocardiogram (ECG): measuring the electrical activity of the heart

5. Urine sample for standard laboratory tests
6. Blood samples for standard laboratory tests and to measure study treatment levels (pharmacokinetics)
7. Tumor tissue samples (biopsies)
8. Tumor assessments: scans of the internal organs and bones that may include a computed tomography (CT) scan, a magnetic resonance imaging (MRI) scan, or a bone scan
9. Eye examination

What are the possible benefits and risks of participating?
The patient's cancer and health may or may not improve in this study, but the information collected may help other people who have a similar medical condition in the future.
High blood sugar, oral inflammation/ulcers, rash, and diarrhea/colitis (colon inflammation) are identified risks for inavolisib. Pneumonitis (lung inflammation), immunosuppressant effects, reproductive effects, eye toxicities, and embryo-fetal toxicities are potential risks for inavolisib. Results to date have shown good tolerability, with no additional safety concerns beyond those associated with expected toxicities. Paclitaxel is known to cause decrease in the activity of the gelatinous tissue that fills the cavities, or the centers of bones (bone marrow suppression), hypersensitivity reactions, joint or muscle pain, oral inflammation/ulcers, nerve damage, alopecia (hair loss), injection site reactions, and vascular (blood vessel) disorders. Given that these risks may require either dose interruptions and/or dose reductions or may have the potential to cause life-threatening conditions, close monitoring and a robust risk-mitigation strategy will be implemented during this study. Since immunosuppressant effects are a potential risk for inavolisib and bone marrow suppression is very commonly associated with the use of paclitaxel, a possible consequence of immunosuppression may be an increased susceptibility to acute infections including COVID-19. At this time, there is insufficient evidence for a causal association between inavolisib and an increased risk of severe outcomes from COVID-19. Pneumonitis (lung inflammation) is a potential risk for inavolisib and a few cases of Grade 1, 2 pneumonitis have been observed after treatment with inavolisib. There may be a potential overlap in clinical and radiological features for inavolisib-induced pneumonitis and COVID-19-related interstitial pneumonia. Available non-clinical and clinical data for inavolisib support the proposed evaluation of inavolisib in combination with paclitaxel in solid tumors in this study. Considering the known safety profiles of inavolisib and paclitaxel and the safety risk mitigation measures incorporated in this study, it is anticipated that the combination treatments in this study will have a manageable safety profile and an acceptable benefit-risk assessment for the conduct of the study.

Where is the study run from?
Genentech, Inc (USA)

When is the study starting and how long is it expected to run for?
July 2020 to October 2025

Who is funding the study?
Genentech, Inc (USA)

Who is the main contact?
global-roche-genentech-trials@gene.com

Contact information

Type(s)

Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-005057-24

Protocol serial number
CO42800

Study information

Scientific Title
A Phase Ib, open-label, dose-escalation and dose-expansion study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of inavolisib in combination with paclitaxel in patients with locally advanced or metastatic solid tumors

Study objectives
Current study hypothesis as of 20/07/2022:
The aim is to evaluate the safety, pharmacokinetics, pharmacodynamic (PD) effects, and preliminary anti-tumor activity of inavolisib administered in combination with paclitaxel in patients with locally advanced or metastatic solid tumors and locally advanced or metastatic PIK3CA-mutated, HER2-positive breast cancer.

Previous study hypothesis:
The aim is to evaluate the safety, pharmacokinetics, pharmacodynamic (PD) effects, and preliminary anti-tumor activity of inavolisib administered in combination with paclitaxel in patients with locally advanced or metastatic solid tumors, and of inavolisib administered in combination with paclitaxel, trastuzumab and pertuzumab in patients with locally advanced or metastatic PIK3CA-mutated, HER2-positive breast cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 29/04/2021, Narodowy Instytut Onkologii Im. M. Sklodowskiej-Curie; Oddzial Badan Wczesnych Faz, Ethics Board (Komisja Bioetyczna przy Narodowym Instytucie Onkologii im. M. Sklodowskiej-Curie ul. W.K. Roentgena 5, 02-781 Warszawa, Poland; +48 (0)22 546 33 60, email: not applicable), ref: not applicable

2. Approved 23/04/2021, START Madrid. Centro Integral Oncologico Clara Campal; CIOCC Ethics Board (Comité de Ética de Investigación Clínica HM Hospitales Avda. Montepríncipe, 25, 28660, Boadilla del Monte, Madrid, Spain; +34 (0)91 708 99 00 Ext 2588; secretariaceic@hmhospitales.com), ref: not applicable

Primary study design
Interventional

Study design
Open-label multicenter phase Ib study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Solid tumors, Breast cancer

Interventions
Current interventions as of 20/07/2022:
The study is an open-label design and the treatments include:
Inavolisib - 6 mg/9 mg taken orally every day and potentially on an intermittent weekly schedule of 6/1 or 5/2, until disease progression or unacceptable toxicity.
Paclitaxel - Intravenous infusion 80 mg/m² dose weekly, until disease progression or unacceptable toxicity.

Up to 104 patients at various hospital locations around the world will take part in this study. The study is divided into two parts. Part 1, Arm A is the dose-escalation (dose-finding) part of the study. Part 2, Arm A which will be treatment expansion after dose-finding is complete. Participants will be allocated to the different treatments based on inclusion and exclusion criteria for Part 1 and Part 2:
Part 1, Arm A: inavolisib will be tested at different doses and schedules in combination with paclitaxel in up to 24 patients with locally advanced or metastatic cancer
Part 2, Arm A: a dose and schedule of inavolisib determined to be safe in Part 1, Arm A will be tested in combination with paclitaxel, in approximately 80 patients with locally advanced or metastatic PIK3CA mutated (altered gene) cancer. Participants will be enrolled into four cohorts depending on the tumor type: PIK3CAmutated Head and neck squamous cell carcinoma (HNSCC) (Cohort 1), ovarian cancer (Cohort 2), triple-negative breast cancer (TNBC) (Cohort 3), and endocrine-resistant/refractory positive, HER2 negative breast cancer (Cohort 4).

Patients will have the following assessments and measurements:
1. Vital signs - temperature, pulse rate, blood pressure, breathing rate and oxygen level
2. Complete or limited physical exam
3. Assessment of performance status (Eastern Cooperative Oncology Group daily functioning)
4. Electrocardiogram (ECG)
5. Urine sample for standard laboratory tests
6. Blood samples for standard laboratory tests and to measure pharmacokinetics
7. Tumor tissue biopsies
8. Tumor assessments: scans of internal organs and bones that may include:
8.1. Computed tomography (CT) scan

8.2. Magnetic resonance imaging (MRI) scan
8.3. Bone scan
9. Eye examination

Previous interventions:
The study is an open-label design and the treatments include:
Inavolisib - 6 mg/9 mg taken orally every day and potentially on an intermittent weekly schedule of 6/1 or 5/2, until disease progression or unacceptable toxicity.
Paclitaxel - Intravenous infusion 80 mg/m² dose weekly, until disease progression or unacceptable toxicity.
Trastuzumab - Intravenous infusion every 3 weeks. Loading dose of 8 mg/kg for Cycle 1 and a dose of 6 mg/kg for subsequent cycles, until disease progression or unacceptable toxicity.
Pertuzumab - Intravenous infusion every 3 weeks. Loading dose of 840 mg for the first cycle and a dose of 420 mg for subsequent cycles, until disease progression or unacceptable toxicity.

Up to 120 patients at various hospital locations around the world will take part in this study. The study is divided into two parts. Part 1, Arm A is the dose-escalation (dose-finding) part of the study. Part 2 consists of Arm A and Arm B, which will be treatment expansions after dose-finding is complete. Participants will be allocated to the different treatments based on inclusion and exclusion criteria for Part 1 and Part 2:
Part 1, Arm A: inavolisib will be tested at different doses and schedules in combination with paclitaxel in up to 24 patients with locally advanced or metastatic cancer
Part 2, Arm A: a dose and schedule of inavolisib determined to be safe in Part 1, Arm A will be tested in combination with paclitaxel, in approximately 76 patients with locally advanced or metastatic PIK3CA mutated (altered gene) cancer.
Part 2, Arm B: a dose and schedule of inavolisib determined to be safe in Part 1, Arm A will be tested in combination with paclitaxel, trastuzumab and pertuzumab in approximately 20 patients with locally advanced or metastatic PIK3CA-mutated (altered gene) HER2 positive breast cancer

Patients will have the following assessments and measurements:
1. Vital signs - temperature, pulse rate, blood pressure, breathing rate and oxygen level
2. Complete or limited physical exam
3. Assessment of performance status (Eastern Cooperative Oncology Group daily functioning)
4. Electrocardiogram (ECG)
5. Urine sample for standard laboratory tests
6. Blood samples for standard laboratory tests and to measure pharmacokinetics
7. Tumor tissue biopsies
8. Tumor assessments: scans of internal organs and bones that may include:
8.1. Computed tomography (CT) scan
8.2. Magnetic resonance imaging (MRI) scan
8.3. Bone scan
9. Eye examination

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)

Inavolisib, paclitaxel

Primary outcome(s)

Safety Objectives:
1. Incidence and nature of dose-limiting toxicities (Part 1 only) measured using adverse events (graded by NCI CTCAE v5.0) recorded within the first 28 days (cycle 1) of study treatment
2. Incidence, type, and severity of adverse events including serious adverse events graded by NCI CTCAE v5.0 recorded throughout the study
3. Targeted vital signs measured using standard techniques assessed by site staff at baseline and weekly/monthly during study treatment
4. Targeted clinical laboratory test results measured using standard hospital laboratory analyses at baseline and taken every week/cycle, including ECGs, recorded by taken by site staff at baseline and every cycle during study treatment

Key secondary outcome(s)

Current secondary outcome measures as of 20/07/2022:
Pharmacokinetic Objective (Secondary Objective):
Plasma concentration of inavolisib administered in combination with paclitaxel (Arm A) measured by a bioanalytical laboratory at Cycles 1-3. The following PK parameters will be determined as appropriate:
1. Area under the concentration-time curve (AUC)
2. Maximum plasma concentration (Cmax)
3. Minimum plasma concentration (Cmin)
4. Additional plasma PK parameters as warranted

Activity/Efficacy Objectives (Secondary Objectives):
Preliminary assessment of the anti-tumor activity of:
1. Inavolisib administered in combination with paclitaxel in patients with locally advanced or metastatic PIK3CA-mutated solid tumors (*Part 2 Arm A)

The corresponding endpoints are as follows:
1. Objective response rate (ORR) defined as a complete recovery (CR) or partial recovery (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator through use of RECIST v1.1 every 8(*) weeks during the study treatment
2. Best overall response (BOR) defined as the proportion of patients with a CR or PR, as determined by the investigator through use of RECIST v1.1 every 8(*) weeks during study treatment
3. Duration of response (DOR) defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through the use of RECIST v1.1, or death, whichever occurs first, every 8(*) weeks during study treatment
4. Clinical benefit rate (CBR) defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, or stable disease (SD; non-complete response/non-progressive disease for patients with non-measurable disease at baseline) ≥24 weeks, as determined by the investigator through use of RECIST v1.1 every 8(*) weeks during study treatment
5. Progression-free survival (PFS) defined as the time from the first study treatment (Day 1) to the first occurrence of disease progression, as determined by the investigator through the use of RECIST v1.1 every 8(*) weeks during study treatment, or death, whichever occurs first

Previous secondary outcome measures:
Pharmacokinetic Objective (Secondary Objective):
Plasma concentration of inavolisib administered in combination with paclitaxel (Arm A), or with

paclitaxel, trastuzumab, and pertuzumab (Arm B) measured by a bioanalytical laboratory at Cycles 1-3. The following PK parameters will be determined as appropriate:
1. Area under the concentration-time curve (AUC)
2. Maximum plasma concentration (Cmax)
3. Minimum plasma concentration (Cmin)
4. Additional plasma PK parameters as warranted

Activity/Efficacy Objectives (Secondary Objectives):
Preliminary assessment of the anti-tumor activity of:
1. Inavolisib administered in combination with paclitaxel in patients with locally advanced or metastatic PIK3CA-mutated solid tumors (*Part 2 Arm A)
2. Inavolisib administered in combination with paclitaxel, trastuzumab and pertuzumab in patients with locally advanced or metastatic PIK3CA mutated, HER2-positive breast cancer (#Part 2 Arm B)

The corresponding endpoints are as follows:
1. Objective response rate (ORR) defined as a complete recovery (CR) or partial recovery (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator through the use of RECIST v1.1 every 8(*) or 9(#) weeks during study treatment
2. Best overall response (BOR) defined as the proportion of patients with a CR or PR, as determined by the investigator through the use of RECIST v1.1 every 8(*) or 9(#) weeks during study treatment
3. Duration of response (DOR) defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through use of RECIST v1.1, or death, whichever occurs first, every 8(*) or 9(#) weeks during study treatment
4. Clinical benefit rate (CBR) defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, or stable disease (SD; non-complete response/non-progressive disease for patients with non-measurable disease at baseline) ≥24 weeks, as determined by the investigator through use of RECIST v1.1 every 8(*) or 9(#) weeks during study treatment
5. Progression-free survival (PFS) defined as the time from the first study treatment (Day 1) to the first occurrence of disease progression, as determined by the investigator through the use of RECIST v1.1 every 8(*) or 9(#) weeks during study treatment, or death, whichever occurs first

Completion date
30/10/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/07/2022:
1. Signed Informed Consent Form
2. Aged over 18 years and over
3. Evaluable or measurable disease per RECIST, v1.1
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Life expectancy of >12 weeks
6. Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:
6.1. Absolute neutrophil count 1500/µl
6.2. Hemoglobin ≥9 g/dl
6.3. Platelet count ≥100,000/l
6.4. Fasting glucose <126 mg/dL or <7 mmol/l and glycosylated hemoglobin (HbA1C) 5.7% or <39

millimoles per mole (mmol/mol)
6.5. Total bilirubin <1.5 upper limit of normal (ULN)
6.6. Serum albumin ≥2.5 g/dl or 25 g/l
6.7. AST and ALT ≤2.5 ULN with the following exception: patients with documented liver metastases may have AST and ALT ≤5.0 ULN.
6.8. Serum creatinine 1.5 ULN or creatinine clearance ≥50 ml/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation
6.9. International normalized ratio (INR) <1.5 x upper limit of normal (ULN) and activated partial thromboplastin time (aPTT) <1.5 x ULN
7. Consent to provide fresh (preferred) or archival tumor tissue specimen. It is preferred that the specimen be from the most recently collected and available tumor tissue, and whenever possible, from a metastatic site of disease.
8. Consent to provide a freshly collected pre-treatment blood sample.
9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective form of contraceptive method with a failure rate of 1% per year in combination with use of male condom with spermicide (for male partners), unless male sterilization has been confirmed.
10. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive measures, and agreement to refrain from donating sperm.

Inclusion Criteria Specific to Patients Enrolling in Part 1, Arm A:
Histologically documented, locally advanced, recurrent, or metastatic, incurable solid tumor malignancy that has progressed after available standard systemic therapies; or for whom standard therapy has proven to be ineffective or intolerable; or for whom a clinical trial of an investigational agent is a recognized standard of care. If there are other available SOC therapies, these will be discussed with the patient and documented before informed consent is obtained.

Inclusion Criteria Specific to Patients Enrolling in Part 2, Arm A Expansion Cohorts:
1. Histologically documented, locally advanced, recurrent, or metastatic, incurable solid tumor malignancy with a known PIK3CA mutation that has progressed after at least one available standard systemic therapy in the metastatic setting.
– Cohort 1 (HNSCC): Histologically or cytologically confirmed recurrent and/or metastatic HNSCC that has been previously treated with systemic therapy in the recurrent and/or metastatic setting, which may include immunotherapy and/or chemotherapy with or without cetuximab.
– Cohort 2 (ovarian cancer): Persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal tumors that have been previously treated with up to 4 prior regimens in the recurrent and/or metastatic setting, being at least one platinum-based. Patients may have received bevacizumab and/or poly-ADP ribose polymerase (PARP) inhibitors.
– Cohort 3 (TNBC): Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic, not amenable to surgical or radiation therapy with curative intent, which has progressed after all available standard therapies, or for which standard therapy has proven to be ineffective or intolerable.
– Cohort 4 (endocrine resistant/refractory HR-positive, HER2 negative breast cancer): Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or radiation therapy with curative intent and has progressed after all available endocrine-based standard therapies in the locally advanced /metastatic setting or for which endocrine-based standard therapy has proven to be ineffective or intolerable.
2. Confirmation of biomarker eligibility: valid results from central testing of blood or local testing of blood or tumor tissue documenting PIK3CA-mutated tumor status is required for patients enrolling to Part 2, Arm A, expansion cohorts.

Previous inclusion criteria:
1. Signed Informed Consent Form
2. Aged over 18 years and over
3. Evaluable or measurable disease per RECIST, v1.1
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Life expectancy of 12 weeks
6. Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:
6.1. Absolute neutrophil count 1500/l
6.2. Hemoglobin 9 g/dl
6.3. Platelet count 100,000/l
6.4. Fasting glucose 126 mg/dL or 7 mmol/l and glycosylated hemoglobin (HbA1C) 5.7%
6.5. Total bilirubin 1.5 upper limit of normal (ULN)
6.6. Serum albumin 2.5 g/dl or 25 g/l
6.7. AST and ALT 2.5 ULN with the following exception: patients with documented liver metastases may have AST and ALT 5.0 ULN.
6.8. Serum creatinine 1.5 ULN or creatinine clearance 50 ml/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation
6.9. International normalized ratio (INR) <1.5 x upper limit of normal (ULN) and activated partial thromboplastin time (aPTT) <1.5 x ULN
7. Consent to provide fresh (preferred) or archival tumor tissue specimen. It is preferred that the specimen be from the most recently collected and available tumor tissue, and whenever possible, from a metastatic site of disease. See the laboratory manual and Section 4.5.7 for specimen requirements.
8. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective form of contraceptive method with a failure rate of 1% per year in combination with use of male condom with spermicide (for male partners), unless male sterilization has been confirmed.
9. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive measures, and agreement to refrain from donating sperm.

Inclusion Criteria Specific to Patients Enrolling in Part 1, Arm A:
Histologically documented, locally advanced, recurrent, or metastatic, incurable solid tumor malignancy that has progressed after available standard systemic therapies; or for whom standard therapy has proven to be ineffective or intolerable; or for whom a clinical trial of an investigational agent is a recognized standard of care. If there are other available SOC therapies, these will be discussed with the patient and documented before informed consent is obtained.

Inclusion Criteria Specific to Patients Enrolling in Part 2, Arm A Expansion Cohorts:
1. Histologically documented, locally advanced, recurrent, or metastatic, incurable solid tumor malignancy with a known PIK3CA mutation that has progressed after at least one available standard systemic therapy in the metastatic setting.
2. Confirmation of biomarker eligibility: valid results from central testing of blood or local testing of blood or tumor tissue documenting PIK3CA-mutated tumor status is required for patients enrolling to Part 2, Arm A, expansion cohorts.

Inclusion Criteria Specific to Patients Enrolling in Part 2, Arm B:
1. Patients with histologically documented locally advanced or metastatic PIK3CA-mutated HER2-positive breast cancer
2. Patients may present with either: de novo metastatic HER2-positive disease for which they have not received any systemic HER2-positive anti-cancer treatment recurrent locally advanced or metastatic disease following prior HER2-positive targeted treatment for early breast cancer,

where the diagnosis has been based on the biopsy of the locally recurrent or metastatic disease and the patient has progressed following (neo)adjuvant HER2-positive targeted therapy with a treatment-free interval of 6 months
3. Documented HER2-positive and either HR-positive or HR-negative breast cancer according to ASCO/CAP guidelines based on local assessment HER2-positive
4. Confirmation of biomarker eligibility: valid results from central testing of blood documenting PIK3CA-mutated tumor status is required for patients enrolling to Part 2, Arm B
5. Patients may have received prior paclitaxel and HER2directed therapies in the (neo)adjuvant setting, including trastuzumab and pertuzumab, as long as the patients did not discontinue prior paclitaxel, prior trastuzumab, or pertuzumab because of a toxicity assessed as related to one or more of these agents
6. Left ventricular ejection fraction (LVEF) 50%, as determined by either echocardiography (ECHO) (preferred) or multiple gated acquisition (MUGA) scan, at screening
7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective form of contraceptive method with a failure rate of 1% per year, and agreement to refrain from donating eggs, during the treatment period and for at least 60 days after the last dose of inavolisib, at least 6 months after the last dose of paclitaxel, at least 7 months after the last dose of pertuzumab and the last dose of trastuzumab.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Metaplastic breast cancer
2. Any history of leptomeningeal disease
3. Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
4. Inability or unwillingness to swallow pills
5. Malabsorption syndrome or other condition that would interfere with enteral absorption
6. Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).
7. Uncontrolled pleural effusion or ascites requiring recurrent drainage procedures twice per month or more frequently
8. Any active infection that, in the opinion of the investigator, could impact patient safety; or, serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1
9. Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator or study ophthalmologist, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition

10. Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmuneassociated uveitis in either eye
11. Patients requiring any daily supplemental oxygen
12. History of or active inflammatory disease (e.g., Crohn's disease or ulcerative colitis), or any active bowel inflammation (including diverticulitis). Patients currently receiving immunosuppressants (e.g., sulfasalazines) are considered to have active disease; therefore, they are ineligible.
13. Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy
14. Clinically significant history of liver disease, including severe liver impairment (Child-Pugh Class B/C), viral or other hepatitis, current alcohol abuse, or cirrhosis
15. Known HIV infection
16. Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
17. Significant traumatic injury or major surgical procedure within 4 weeks prior to initiation of study treatment
18. Radiation therapy (other than palliative radiation to bony metastases) as cancer therapy within 4 weeks prior to initiation of study treatment
19. Palliative radiation to bony metastases within 2 weeks prior to initiation of study treatment
20. Unresolved toxicity from prior therapy, except for the following: Alopecia Grade 1 and peripheral neuropathy
21. Inability to comply with study and follow-up procedures
22. History of other malignancy within 5 years prior to screening, with the exception of patients with a negligible risk of metastasis or death and/or treated with expected curative outcome (such as appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)
23. History of or active ventricular dysrhythmias or congestive heart failure requiring medication or coronary heart disease that is symptomatic
24. Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
25. Congenital long QT syndrome or QT interval corrected with Fridericia's formula (QTcF) 470 ms demonstrated by at least two ECGs 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
26. Current treatment with medications that are well known to prolong the QT interval
27. Allergy or hypersensitivity to components of the inavolisib formulation and paclitaxel
28. Pregnancy, lactation, or intention to become pregnant or fathering a child during the study
29. Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

Exclusion Criteria Specific to Patients Enrolling Part 1, Arm A:
1. History of prior significant toxicity related to a PI3K, AKT, or mTOR inhibitor requiring discontinuation of treatment. Patients may have received prior treatment with a PI3K, AKT, or mTOR inhibitor
2. History of prior significant toxicity related to paclitaxel treatment requiring discontinuation of treatment. Patients may have received prior treatment with paclitaxel
3. Treatment with chemotherapy, immunotherapy, or biologic therapy as anti-cancer therapy within 21 days prior to initiation of study treatment, except for the following: Kinase inhibitors, approved by regulatory authorities, may be used up to 2 weeks prior to initiation of study treatment, provided any drug-related toxicity has resolved up to Grade 1 and prior approval is

obtained from the Medical Monitor. Treatment with an investigational agent within 3 weeks or five half-lives prior to initiation of study treatment, whichever is shorter. A shorter washout period may be allowed if the patient has adequately recovered from any clinically relevant toxicity and with prior approval from the Medical Monitor.
4. Prior anti-cancer therapy that fulfills the following criteria: High dose chemotherapy requiring stem-cell support; Irradiation to 25% of bone marrow-bearing areas

Exclusion Criteria Specific to Patients Enrolling Part 2, Arm A:
1. History of prior significant toxicity related to a PI3K, AKT, or mTOR inhibitor requiring discontinuation of treatment.
2. Prior treatment with any PI3K-specific inhibitor
3. History of prior significant toxicity related to paclitaxel treatment requiring discontinuation of treatment. Patients may have received prior treatment with paclitaxel
4. Treatment with chemotherapy, immunotherapy, or biologic therapy as anti-cancer therapy within 21 days prior to initiation of study treatment, except for the following: Kinase inhibitors, approved by regulatory authorities, may be used up to 2 weeks prior to initiation of study treatment, provided any drug-related toxicity has resolved up to Grade 1 and prior approval is obtained from the Medical Monitor Treatment with an investigational agent within 3 weeks or five half-lives prior to initiation of study treatment, whichever is shorter
5. Prior anti-cancer therapy that fulfills the following criteria: high dose chemotherapy requiring stem-cell support Irradiation to 25% of bone marrow-bearing areas

Removed 20/07/2022:
Exclusion Criteria Specific to Patients Enrolling Part 2, Arm B:
1. Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K/AKT/mTOR pathway
2. Any prior systemic anti-cancer therapy for locally advanced or metastatic HER2-positive breast cancer prior to initiation of study treatment
3. Current uncontrolled hypertension (systolic blood pressure over 150 mmHg or diastolic blood pressure over 100 mmHg) or unstable angina
4. History of congestive heart failure (CHF) of New York Heart Association (NYHA) classification Class II or higher, or serious cardiac arrhythmia requiring treatment (excluding atrial fibrillation or paroxysmal supraventricular tachycardia)
5. History of myocardial infarction within 6 months prior to initiation of study treatment
6. History of LVEF decline to below 40% during or after prior treatment with trastuzumab
7. History of exposure to cumulative dose of doxorubicin (or equivalent anthracycline exposure) 360 mg/m² of body surface area or its equivalent
8. Symptomatic active lung disease, including pneumonitis or interstitial lung disease
9. History of prior significant toxicity related to paclitaxel, trastuzumab or pertuzumab requiring discontinuation of treatment

Date of first enrolment
26/07/2021

Date of final enrolment
30/11/2024

Locations

Countries of recruitment
Brazil

Canada

Denmark

France

Korea, South

Spain

United States of America

Study participating centre
Florida Cancer Specialist-Lake Mary
805 Currency Circle
Lake Mary
United States of America
32746

Study participating centre
Rigshospitalet
Fase 1 Enhed - Onkologi
Juliane Maries Vej 6
Opgang 5, 1. sal, Afsnit 5011
København Ø
Denmark
2100

Study participating centre
Centre Leon Berard
Departement Oncologie Medicale
28 Rue Laennec
CEDEX 08
Lyon
France
69008

Study participating centre
Institut Bergonie
Oncologie
229 Cours de L'Argonne

Bordeaux
France
33076

Study participating centre
Samsung Medical Center
81, Irwon-Ro, Gangnam-gu
Seoul
Korea, South
(0)6351

Study participating centre
Seoul National University Hospital
101, Daehakro
Jongno-gu
Seoul
Korea, South
03080

Study participating centre
Hospital Clinico Universitario de Valencia
Servicio de Onco-hematologia
Avenida Blasco Ibañez, 17
Valencia
Spain
46010

Study participating centre
Hospital Univ Vall d'Hebron
Servicio de Oncologia
Passeig De La Vall D'hebron 119-129
Barcelona
Spain
08035

Study participating centre
Massachusetts General Hospital
55 Fruit Street
Boston
United States of America
02114

Study participating centre
Sarah Cannon Cancer Center - Tennessee Oncology, PLLC
250 25th Ave North
Suite 312
Nashville
United States of America
37203

Study participating centre
Jewish General Hospital
3755 Côte Ste Catherine Road
Montreal
Canada
H3T 1E2

Study participating centre
Princess Margaret Cancer Centre
700 University Avenue 7th Floor
7723
Toronto
Canada
M5G 1Z5

Study participating centre
START Madrid. Centro Integral Oncologico Clara Campal; CIOCC
-
Madrid
Spain
28050

Study participating centre
Clinica de Pesquisa e Centro de Estudos em Oncologia Ginecologica e Mamaria Ltda
Sao Paulo
Brazil
01317-001

Study participating centre

Núcleo de Pesquisa São Camilo; Oncologia Clinica/Quimioterapia
Sao Paulo
Brazil
04014-002

Study participating centre
Hospital Sao Lucas - PUCRS
Porto Alegre
Brazil
90610-000

Study participating centre
Hospital das Clinicas - UFRGS
Porto Alegre
Brazil
90035-903

Study participating centre
Avera Cancer Institute
Sioux Falls
United States of America
57105

Study participating centre
Hospital do Cancer de Pernambuco - HCP
Recife
Brazil
50040-00

Study participating centre
Hospital Nossa Senhora da Conceicao
Porto Alegere
Brazil
90040-373

Sponsor information

Organisation
Genentech, Inc

Funder(s)

Funder type
Industry

Funder Name
Genentech

Alternative Name(s)
Genentech, Inc., Genentech USA, Inc., Genentech USA

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
Participant level data is not expected to be made available. This is not a regulatory requirement and typically not disclosed for Phase I studies.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes